Antimicrobial combination therapies: a network perspective

P. Jorge[1], M. O. Pereira[1] and **A. Lourenço[1,2]**

[1]CEB - Centre of Biological Engineering, University of Minho, Campus de Gualtar, 4710-057 Braga, Portugal
[2]ESEI - Escuela Superior de Ingeniería Informática, Edificio Politécnico, Universidad de Vigo, Campus Universitario As Lagoas s/n, 32004 Ourense, Spain

The growing number of resistant strains and biofilm-related infections emerging in healthcare settings and in the general community is a major biomedical concern. Currently, antimicrobial studies are revisiting the potential of old products and looking for new products with alternative modes of action. Most notably, antimicrobial peptides (AMPs) are receiving a lot of attention because of the widespread availability, multiple mechanisms of action, non-specific molecular targets, and anti-biofilm capabilities [1], [2].

Considering that most of the results obtained in these studies lay in scientific literature, and manual curation is time and resource consuming, the development of bioinformatics approaches for the systematic screening of the literature is of obvious interest. In particular, the reconstruction of drug interaction networks reflecting *in vitro* and *in vivo* results is considered useful to identify the most promising candidates for the development of alternative antimicrobial therapies, such as antimicrobial combinations [3], [4]. Such networks can aid in profiling and interpreting the activity of AMPs and the added value of antimicrobial combinations, and thus, help exploit their potential.

As a first contribution to this line of analysis, this work presents a novel network reconstruction for results obtained by AMP-drug combinations in fighting *Pseudomonas aeruginosa* infections [5]. This network contains information about strains, combination methodologies, mode of growth, compound description (with drug and AMP database cross-linking) and quantification values (MICs, FICs, log reduction, etc.). So far, the network comprises 239 combinations, such that 83 % of the interactions pair an AMP with a non-AMP compound (antibiotics, enzymes, etc.), mainly traditional antibiotics. The majority (82 %) of the studies focused on the use of combinations on planktonic cells, and surprisingly enough, only 3 % of the studies tested the combination in biofilms. Furthermore, the network is dominated by a small number of highly connected nodes, namely the peptides colistin and polimyxin B. These are the products that are more often tested in antimicrobial combinations.

The network is publicly available, and may be further explore using graph-based analysis tools. Hopefully, this will be a valuable resource to the design of new experiments, unveiling different mechanisms of action and helping in the prediction of new combinations.

Keywords: antimicrobial peptides (AMPs); *Pseudomonas aeruginosa*; biofilms; network; bioinformatics

References

[1] P. Jorge, A. Lourenço, and M. O. Pereira, “New trends in peptide-based anti-biofilm strategies : a review of recent achievements and bioinformatic approaches,” *Biofouling*, vol. 28, no. November, pp. 1033–1061, 2012.
[2] F. Guilhelmelli, N. Vilela, P. Albuquerque, L. da S. Derengowski, I. Silva-Pereira, and C. M. Kyaw, “Antibiotic development challenges: the various mechanisms of action of antimicrobial peptides and of bacterial resistance.,” *Front. Microbiol.*, vol. 4, p. 353, Jan. 2013.
[3] M. A. Fischbach, “Combination therapies for combating antimicrobial resistance.,” *Curr. Opin. Microbiol.*, vol. 14, no. 5, pp. 519–23, Oct. 2011.
[4] L. Saiman, “Clinical utility of synergy testing for multidrug-resistant Pseudomonas aeruginosa isolated from patients with cystic fibrosis: ‘the motion for,’” *Paediatr. Respir. Rev.*, vol. 8, no. 3, pp. 249–255, 2007.
[5] P. Jorge, M. O. Pereira, and A. Lourenço, “Networking the Way towards Antimicrobial Combination Therapies,” in *Advances in Intelligent and Soft Computing*, J. Kacprzyk, Ed. Springer, 2014.

Acknowledgements: The authors thank the project PTDC/SAU-ESA/646091/2006/FCOMP-01-0124-FEDER-007480FCT, the Strategic Project PEst-OE/EQB/LA0023/2013, the Project “BioHealth - Biotechnology and Bioengineering approaches to improve health quality", NORTE-07-0124-FEDER-000027, co-funded by the Programa Operacional Regional do Norte (ON.2 – O Novo Norte), QREN, FEDER, the project “RECI/BBB-EBI/0179/2012 - Consolidating Research Expertise and Resources on Cellular and Molecular Biotechnology at CEB/IBB”, FCOMP-01-0124-FEDER-027462, and the Agrupamento INBIOMED from DXPCTSUG-FEDER unha maneira de facer Europa (2012/273). The research leading to these results has received funding from the European Union's Seventh Framework Programme FP7/REGPOT-2012-2013.1 under grant agreement n° 316265, BIOCAPS. This document reflects only the author’s views and the European Union is not liable for any use that may be made of the information contained herein. The authors also acknowledge the PhD Grant of Paula Jorge, Ref. SFRH/BD/88192/2012.